

**How Safe Is Universal Hepatitis B Vaccination?**

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## INTRODUCTION

Universal hepatitis B vaccination of infants in the United States, regardless of risk factors, was first proposed by Margolis and his coworkers of the hepatitis branch of the Center for Disease Control and Prevention in Atlanta, Georgia.<sup>(1,2)</sup> The concept was endorsed and augmented by West and his coworkers at the Merck Sharpe and Dohme research laboratories in West Point, Pennsylvania.<sup>(3)</sup> The rationale presented for universal vaccination of infants in the U.S. stemmed from the failure of the current strategies for controlling this disease and not from trials that demonstrated the effectiveness or safety of a universal hepatitis B vaccination program.<sup>(4,5)</sup> In spite of this, universal hepatitis B vaccination is achieving wide spread acceptance among medical organizations and is being vigorously pursued in many sections of the country.<sup>(5,6)</sup>

To be presented here are four patterns that raise some concerns about vaccinating all babies in the U.S. with the hepatitis B vaccine. The patterns are as follows: The historical pattern of events that followed the introduction of an antirabies vaccine in the late 1800's and of warnings regarding probable occurrence of vaccine complications given by medical scientists during the past 50 years; the pattern revealed by animal experimentation that showed that viruses and viral particles may cause demyelination and autoimmunity in a variety of species; the pattern of autoimmunity and demyelination that has been caused by the hepatitis B infection, itself; the pattern of clinical reports that reveal that demyelination and autoimmunity have appeared in patients vaccinated with hepatitis B vaccines.

Reasonable steps that might be taken to address the concerns evoked by the above patterns will be discussed.

### **Postvaccinal Encephalomyelitis and Warnings by Medical Scientists**

Postvaccinal encephalomyelitis has been recognized and accepted as a clinical entity since it first occurred after Pasteur's antirabies vaccine was used.<sup>(7)</sup> At first the encephalomyelitis was thought to be caused by the nervous tissue in which the virus used for the vaccine was grown.<sup>(7)</sup> However, postvaccinal encephalomyelitis has appeared in patients who received vaccine grown in duck eggs, so it is now thought that the syndrome is caused by something present in the dead virus.<sup>(8)</sup> Postvaccinal encephalomyelitis has since been observed after a wide variety of vaccinations.

Within the past 30 years representatives of the medical establishment have discussed and warned about neurologic complications of various vaccines.<sup>(9-12)</sup> Wilson, in his 1967 monograph regarding vaccine complications, pointed out that there are no insurance policies without premiums and that strict attention must be paid to the premiums exacted by each vaccine.<sup>(9)</sup> Miller, in 1954, discussed the neurologic sequelae of vaccination and the difficulty of these complications being recognized and accepted.<sup>(10)</sup> Zuckerman, in an article in 1974 in *Nature* entitled "Hepatitis Vaccine: A note of caution" pointed out that autoimmunity might well follow the hepatitis B vaccinations because the disease, itself, involved autoimmunity.<sup>(11)</sup> He suggested, "careful assessment of all vaccine effects on the immune system."<sup>(11)</sup> As late as 1988, Hilleman, who some call the "father" of hepatitis B vaccine, warned "the message from the hypothetical hepatitis B example is that the administration of antigens or monoclonal antibodies that

directly or indirectly raise antibodies that attach to host cell receptors may carry large liabilities even though they might provide a convenient means for preventing viral access to host cells... antibodies attached to cell receptors may invite the same kinds of adverse response that are believed to be responsible for a variety of autoimmune disorders."<sup>(12)</sup>

### **Experiments In Animals That Lead To Concerns about the Hepatitis B Vaccine**

Experiments done on animals in the past 60 years have yielded data that add to the concerns about present day viral vaccines. These experiments have shown that polypeptide chains of the types found in viruses that are homologous or nearly homologous with myelin can cause demyelination and have shown that viruses, themselves, can cause demyelination.<sup>(13)</sup>

The experiments started in 1956 when Rivers showed that myelin injected into monkeys caused demyelination.<sup>(14)</sup> Wakesman expanded these studies and developed an experimental model in which myelin and adjuvant consistently caused demyelinating disease in mice and rabbits.<sup>(15)</sup> This has been widely accepted as a model for demyelinating diseases in humans and is called experimental allergic encephalomyelitis (EAE).<sup>(16)</sup> Stohlman found that a DNA virus called JHM could cause demyelination in mice.<sup>(17)</sup> Oldstone then presented experimental evidence that autoimmunity in humans was caused by polypeptides in viruses that were homologous to those in human tissue.<sup>(18)</sup> Fujinami and Oldstone produced EAE in rabbits with proteins from hepatitis B virus that had polypeptides in it that were homologous with myelin.<sup>(19)</sup> Ziegler produced EAE in rabbits with the Swine Flu Vaccine and adjuvants.<sup>(20)</sup>

Westall and Root-Bernstein presented data that suggested a syndrome they called Multiple-Antigen-Mediated-Autoimmunity (MAMA) could occur in animals and humans.<sup>(21)</sup> They postulated that the MAMA Syndrome was operative in postvaccinal encephalomyelitis as well as in EAE.<sup>(21)</sup> Root-Bernstein hypothesized that this syndrome could occur in humans if four conditions were met. The first was demonstrated homology between an antigen and host tissue. The second was the presence simultaneously, of more than one antigen. The third was complementarity between the antigens shown to be present. The fourth was the additional presence of a bacterial adjuvant. As will be discussed later, all of these requirements can be tested for as a possible explanation for post hepatitis B vaccine reactions.

Finally, the HLA patterns of experimental animals has been shown to influence their susceptibility to experimental demyelinating diseases.<sup>(22)</sup>

### **Hepatitis B Infection Causes Autoimmunity and Demyelination**

Another group of patterns regarding the consideration of universal hepatitis vaccination, without factoring in risk factors that have been largely ignored, are those revealed by the findings that the infection, itself, causes autoimmunity and demyelination. In 1977, London first reported that autoimmune disease was caused by circulating immune complexes caused by viral antibody association.<sup>(23)</sup> In 1987, Tsukada reported demyelinating neuropathy associated with the hepatitis B

infection.<sup>(24)</sup> Discussions and case reports regarding autoimmunity occurring with the hepatitis B infection have been presented by Vento et al and McFarlane et al.<sup>(25,26)</sup> As early as 1976, Zuckerman cautioned that since autoimmunity is involved in the pathogenesis of hepatitis B infections that it might be augmented by a hepatitis B vaccination.<sup>(11)</sup>

### **Reports Of Demyelination and Autoimmunity After Hepatitis B Vaccination**

Clinical experiences since the general release of hepatitis B vaccines suggest that clinical counterparts of the animal studies and autoimmunity that occurs after the hepatitis B infection occur after hepatitis B vaccination. The first report of demyelination after the hepatitis B vaccination was that of Ribera and Dutka in 1983. The complication was transient.<sup>(27)</sup> The authors stated inflammatory polyradiculoneuropathies after both viral diseases and vaccinations have been widely reported.<sup>(27)</sup> They emphasized the necessity of continued surveillance of the use of hepatitis B vaccine.<sup>(27)</sup> I have noted seven cases of a neurologic picture resembling multiple sclerosis (MS) after hepatitis B vaccination.<sup>(28)</sup> In 1987, Fried et al reported uveitis that occurred in a 20-year-old nurse after a booster dose of hepatitis B vaccine.<sup>(29)</sup> They pointed out that there is a higher than normal level of hepatitis B antibodies in some uveitis patients. They postulated that these antibodies combined with surface antigens in the vaccine could form a disease producing immune complex.<sup>(29)</sup>

Shaw et al reported a post marketing surveillance study regarding neurologic events after the hepatitis B vaccine in 1988.<sup>(30)</sup> An estimated 850,000 individuals had received the vaccine by the time of their

study. They found ten cases of Bell's palsy, nine cases of Guillain-Barre Syndrome, five cases of lumbar radiculopathy, three cases of brachial plexus neuropathy, five cases of optic neuritis, and four cases of transverse myelitis. They concluded, on the basis of the controversial epidemiologic methods used to study the Swine Flu epidemic of 1976, that the risk of the vaccine was outweighed by the prophylactic benefits in "high risk groups."<sup>(30,31)</sup> However, even using these methods, they concluded that the demyelinating disease, Guillain-Barre Syndrome, occurred more often in individuals who had been vaccinated than in the general population.<sup>(30)</sup> In 1988, Biron et al reported a case of myasthenia gravis that occurred after anesthesia and a hepatitis B vaccination.<sup>(32)</sup> They postulated that the autoimmune disease was due to the "challenge" to the immune system by the vaccine.<sup>(32)</sup> In 1989, Goolsby reported a case of erythema nodosum that occurred after recombinant hepatitis B vaccine.<sup>(33)</sup> In 1991, Herroelen et al reported on two patients who developed symptoms of increasing demyelination after a vaccination of recombinant hepatitis B vaccine.<sup>(34)</sup> He mentioned that their HLA patterns might be a contributing factor. Seven hundred reports of adverse reactions to the hepatitis B vaccine were sent in to the Vaccine Adverse Events Reporting Systems (VAERS) between October 1990 and September 1991.<sup>(35)</sup> This system was set up via the National Childhood Vaccine Injury Act of 1986. Sixteen percent of these reports were of damage presumed to be to the myelin of the nervous system. There were 21 cases of facial paralysis and six cases of MS. Eighty-two of the complications occurred in patients who received plasma derived vaccine and 18 occurred in those who received recombinant vaccine.<sup>(35)</sup> This difference can be explained by the fact that at the time the VAERS were examined, the recombinant vaccine had just come into general use. In 1990, in the World Health Organization Drug Information Bulletin two

cases of optic neuritis and one case of Guillain-Barre Syndrome were reported to be among the 200 reports of adverse reactions that were reported by the Australian National Regulatory Body.<sup>(36)</sup> One patient had vertigo and diplopia attributed to demyelination eight months after the vaccination.<sup>(36)</sup>

In 1993, Trevisani et al reported a case of transverse myelitis that followed a recombinant vaccination in an 11 year-old girl.<sup>(37)</sup> Their arguments for a causal link between the vaccination and the transverse myelitis were the temporal association (21 days), the previous report of Shaw's in which the same complication occurred, and no clinical evidence of any other cause of the disease.<sup>(37)</sup> They pointed out that transverse myelitis was occasionally found in patients with hepatitis B.<sup>(37)</sup> This suggested to them that there might be antigenic determinants held in common with the capsular antigen of the hepatitis B vaccine and myelin.<sup>(37)</sup>

In 1993, Nadler et al reported a case of "classic MS," the prodromal of which appeared 10 days after a recombinant vaccination.<sup>(38)</sup> They stated that the benefits of the hepatitis B vaccination, among the population for "which it is usually recommended," far out weigh any potential risks.<sup>(38)</sup> In 1990, there was a report in the British Medical Journal of vasculitis related to the hepatitis B vaccination.<sup>(39)</sup> It was felt to be due to immune complex disease. In 1993, Brezin et al reported visual loss and eosinophilia after a recombinant hepatitis B vaccine.<sup>(40)</sup>



In 1995, Kaplanski et al reported a case of central nervous system demyelination that occurred in a 37-year-old man two weeks after receiving the third hepatitis B injection.<sup>(41)</sup> This patient had the same haplotype as the patient reported by Herroelen.<sup>(34)</sup> They suggested that the hepatitis B vaccination could potentially induce CNS demyelination in patients with HLA, B7, DR2 haplotype, whether or not these patients have a history of MS.<sup>(41)</sup>

Vautier and Carty in 1994 reported a case of classic rheumatoid arthritis that followed a hepatitis B vaccination.<sup>(42)</sup> They brought up the fact that the patient was HLA, DR4 positive which would be consistent with both animal and previous clinical reports regarding complications of the hepatitis B vaccine.<sup>(22,33,42)</sup> Hassan and Oldham reported two cases of reactive arthritis and Reiter's Syndrome that occurred after a recombinant hepatitis B vaccine.<sup>(43)</sup> They cite a personal communication from the manufacturer that stated that in 11 cases reported to them of reactive arthritis following recombinant hepatitis B vaccine that six had a recurrence of symptoms after a second vaccination.<sup>(43)</sup>

In 1995, Tartaglina et al reported a case of postvaccinal myelitis that occurred one month after a hepatitis B vaccination.<sup>(44)</sup> They suggested that complications of this sort may be under reported because there can be a delay in symptom occurrences.<sup>(44)</sup> In the case they reported, symptoms did not occur until one month after a single injection of the vaccine. No other cause of the myelitis was shown by a MRI.<sup>(44)</sup>

## DISCUSSION

**How might the concerns evoked by the material that has been presented be addressed?**

Parents of babies and adolescents who have little chance of being exposed to hepatitis B should be made aware of the potential dangers of the vaccine. A perspective, inclusive, long term follow up study of a large number of individuals who have received the vaccine should be done and the results should be made available to the parents of children who are to be vaccinated. While these admittedly tedious studies are being conducted, databases available through societies such as the Multiple Sclerosis Society might be used to determine if an inordinate number of patients with multiple sclerosis had received a hepatitis B vaccination prior to being diagnosed.

The literally hundreds of individuals who have been reported to VAERS and pharmaceutical companies, who claim to have suffered demyelination and autoimmunity from a hepatitis B vaccine, should be followed up to determine their HLA patterns to ascertain if host factors are partially causative of the complication.<sup>(22,33)</sup>

A large group of individuals who are to be vaccinated should have before and after determinations by the methods of Zhang, Wucherpfennig and Strominger of the percentage of their T-cells that exhibit antimyelin activity to determine if vaccination does evoke such cells in some individuals with certain HLA patterns.<sup>(47,48)</sup>

The ability of vaccines when injected with adjuvant into animals to cause EAE should be tested using the methods of Fujinami and Ziegler.<sup>(19,20)</sup>

The hypothesis and studies of Westall and Root-Bernstein that indicate a multifactorial pathogenesis of postvaccinal encephalomyelitis suggest a series of studies that could be done on vaccines and on patients who developed complications after the hepatitis B vaccination.<sup>(21)</sup> Hepatitis B vaccine and all other vaccines should be tested for the extent of their polypeptide homology with human tissue.<sup>(13,21)</sup> If significant homology were to be demonstrated, the offending polypeptides could be removed from the vaccine or synthetic vaccines could be produced without them.<sup>(49,50)</sup> If such a homology were to be demonstrated, it would fulfill the first requirement for the provocative hypothetical MAMA Syndrome of Westall and Root-Bernstein.<sup>(21)</sup> The second requirement for the MAMA Syndrome is that multiple antigens are present.<sup>(21)</sup> These could be tested for by serologic studies for the Epstein-Barr Virus and other viruses that already have been indicted in this syndrome.<sup>(21)</sup> The third requirement that complementarity between antigens must be demonstrated could be tested for by complementarity studies between the hepatitis B vaccine and other antigens uncovered by the aforementioned serologic tests.<sup>(51)</sup> The fourth requirement that an adjuvant be present could be tested for by serologically determining whether muramyl peptides are present.<sup>(52)</sup> These peptides are well established adjuvants and are ubiquitous as part of the cell walls of all bacteria.<sup>(52)</sup>

The above-mentioned studies might well yield information that would not only make all vaccines safer, but could lead to means to prevent postvaccinal autoimmunity by the methods shown to work in animals by Westall and Root-Bernstein and Norga et al.<sup>(53,54)</sup>

Finally, it should be emphasized that the concerns voiced above in no way denigrate worldwide programs that are attempting to reduce hepatitis B in populations of extremely high risk, both internationally and in the U.S.<sup>(55)</sup> Certainly, there should be no abrupt stopping of present vaccination programs in the U.S., but it does seem reasonable to develop an informed consent that discloses to parents the potential dangers of the vaccine. Parents then would be able to intelligently decide whether the risk involved justifies their child receiving the vaccination. This might be particularly reasonable in areas of the U.S. in which the incidence of hepatitis B is very low.

## REFERENCES

1. Kane, MA, Alter MJ, Hadler SC, Margolis HS. Hepatitis B infection in the United States. Recent trends and future strategies for control. *Am J Med* 1989; 87:11S-13S.
2. Shaprio CN, Margolis HS. Hepatitis B epidemiology and prevention. *Epidemiol Rev* 1990; 12:221-7.
3. West DJ, Margolis HS. Prevention of hepatitis B virus infection in the U.S.: A pediatric perspective. *Pediatr Infect Dis J* 1992; 11:866-74.
4. Margolis HS, Alter MJ, Hadler SC, Margolis HS. Hepatitis B: Evolving epidemiology and implications for control. *Semin Liver Dis* 1991; 11:84-92.
5. American Academy of Pediatrics Committee on Infectious Diseases. Universal hepatitis B immunization. *Pediatrics* 1992; 89:795-800.
6. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991; 40:RR-13, 1-25.
7. Swamy HS, Anisya V, Nandi SS, Kaliaperumal VG. Neurological complications due to semple-type antirabies vaccine. Clinical and therapeutic aspects. *J Assoc Physicians India* 1991; 39(9):667-69.
8. Label LS, Batts DH. Transverse myelitis caused by duck embryo rabies vacc. *Arch Neurol* 1982; 39:426-30.
9. Wilson GS. The hazards of immunization. The Athlone Press. 1967.
10. Miller H, Stanton J. Neurologic sequence of prophylactic inoculation. *Q J Med* 1954; 23:1-27.
11. Zuckerman AJ. Hepatitis Vaccine: A note of caution. *Nature* 1975; 255:104-5.
12. Hilleman MR. Perspectives in the quest for a vaccine against AIDS in 1988 in human retroviruses, in cancer, and AIDs. Approaches to prevention and therapy. P 306. Alan R. Liss Inc., New York.

13. Jahnke U, Fischer EH, Alvord EC Jr. Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. *Science* 1985; 229:282-84.
14. Rivers TM, Schwentker FF. Encephalomyelitis accompanied by myelitis destruction experimentally produced in monkeys. *J Exp Med* 1935; 61:689.
15. Wakesman BH, Adams RD. Allergic neuritis: An experimental disease of rabbits induced by the injection of peripheral nervous system tissue and adjuvants. *J Exp Med* 1955; 102:213-34.
16. Alvord EC, Kies MW, Suckling AJ (eds). *Experimental allergic encephalomyelitis: A useful model for multiple sclerosis*. New York: Liss, 1984.
17. Stohlman SA, Weiner LP. Chronic central nervous system demyelination in mice after JHM virus infection. *Neurology* 1981; 31:38-44.
18. Oldstone MB. Virus induced autoimmunity: Molecular mimicry as a route to autoimmune disease. *J Autoimmun* 1989; 2 suppl:187-94.
19. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin based protein and virus: Mechanism for autoimmunity. *Science*. 1985; 230:1043-45.
20. Ziegler DW, Gardner JJ, Warfield DT, Walls HH. Experimental allergic neuritis-like disease in rabbits after injection with influenza vaccines mixed with gangliosides and adjuvants. *Infect Immun* 1983; 42:824-30.
21. Root-Bernstein RS. Multiple-Antigen-Mediated-Autoimmunity (MAMA) in AIDS: A possible model for post infectious autoimmune complications. *Res Immunol* 1990; 141:321-39.
22. Rose JW. Virus-induced demyelination: From animal models to human disease. *Mayo Clin Proc* 1992; 67:903-6.
23. London WT. Hepatitis B virus and antigen antibody complex diseases. *N Engl J Med* 1977; 296:1528-29.
24. Tsukada N, Koh CS, Inoue A, Yanagisawa N. Demyelinating neuropathy associated with hepatitis B virus infection, detection on immune complexes composed of hepatitis B virus surface antigen. *J Neurol Sci* 1987; 77:203-16.
25. Vento S, Eddleston A. Autoimmunity and liver diseases. *Prog Liver Dis* 1990; 9:335-43.

26. McFarlane BM, Bridger CB, Smith HM, Antonov KA, Naoumov N, Williams R, McFarlane IG. Autoimmune mechanisms in chronic hepatitis B and delta virus infections. *Eur J Gastroenterol and Hepatol* 1995; 7:615-21.
27. Ribera EF, Dutka AJ. Polyneuropathy associated with administration of hepatitis B vaccine (letter). *N Engl J Med* 1983; 309:614-15.
28. Waisbren BA. Other side of the coin (letter). *Inf Dis News* 1992; 5:2.
29. Fried M, Conen D, Conzelmann M., Steinemann E. Uveitis after hepatitis B vaccination (letter). *Lancet* 1987; 2:631-32.
30. Shaw FE Jr, Graham DJ, Guess HA, et al. Post-marketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *AM J Epidemiol* 1988; 127:337-52.
31. Poser CM. Swine influenza vaccination. Truth and consequences. *Arch Neurol* 1985; 42:1090-92.
32. Biron P, Monopetit P, Infante-Rivard C, Lery L. Myasthenia gravis after general anesthesia and hepatitis B vaccine. *Arch Intern Med* 1988; 148:2685.
33. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; 321:1198-99.
34. Herroelen L, de Keyser J, Ebinger G. Central nervous system demyelination after immunization with recombinant hepatitis B vaccine. *Lancet* 1991; 338:1174-75.
35. Data obtained from VAERS through the Freedom of Information Act.
36. Anonymous. Hepatitis B vaccines: Reported reactions. *World Health Organization Adverse Drug Reaction Bulletin*. Aug 1990.
37. Trevisani F, Gattinara GC, Caraceni P, et al. Transverse myelitis following hepatitis B vaccination. *J Hepatol* 1993; 19:317-18.
38. Nadler JP. Multiple sclerosis and hepatitis B vaccination (letter). *Clin Infect Dis* 1993; 17:928-29.

39. Cockwell P, Allen MB, Page R. Vasculitis related to hepatitis B vaccine. *BMJ* 1990; 301:1281.
40. Brezin A, Lautier-Frau M, Hamedani M, Rogeaux O, Hoang PL. Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993; 342:563-4.
41. Kaplanski G, Retornaz F, Durand J, Soubeyrand J. Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. *J Neurol Neurosurg Psychiatry* 1995; 58:758-59.
42. Vautier G, Carty JE. Acute seropositive rheumatoid arthritis occurring after hepatitis vaccination. *Br J Rheumatol* 1994; 33:991.
43. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; 309:94.
44. Tartaglino LM, Heiman-Patherson T, Friedman DP, Flanders AE. MR imaging in a case of postvaccination myelitis. *AJNR Am J Neuroradiol* 1995; 16:581-2.
45. Colditz GA. The nurse's health study: A cohort of US women followed since 1976. *J Am Women's Assoc* 1995; 50:40-4.
46. Glynn RJ, Buring JE, Manson JE, LaMotte F, Hennekens CH. Adherence to aspirin in the prevention of myocardial infarction. The Physicians' Health Study. *Arch Intern Med* 1994; 154:2649.
47. Zhang J, Markovic-Plese S, Lacet B, Raus J, Weiner HL, Hafler DA. Increased frequency of Interleukin-2 responsive T-cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J Exp Med* 1994; 179:973-84.
48. Wucherpfennig KW, Strominger JL. Molecular mimicry in T-cell mediated autoimmunity: Viral peptides activate human T-cell clones specific for myelin basic protein. *Cell* 1995; 80:695-705.
49. Janke U, Fischer EH, Alvord EC Jr. Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. *Science* 1985; 229:282-4.



50. Sela M, Arnon R. Synthetic approaches to vaccines for infectious and autoimmune disease. *Vaccine* 1992; 10:971-6.
51. Westall FC, Robinson AB, Caccam J, et al. Essential chemical requirements for induction of allergic encephalomyelitis. *Nature* 1971; 229:22-24.
52. Hazenberg M.P., de Visser H. Assay for N-acetyluranyl-L-alanine amidase in serum by determination of muramic acid released from the peptidoglycan of *Brevibacterium diviticulum*. *Eur J Clin Chem Biochem* 1992; 30:141-44.
53. Westall FC, Root-Bernstein RS. Cause and prevention of postinfectious and postvaccinal neuropathies in light of a new theory of autoimmunity. *Lancet* 1986; 2:251-2.
54. Norga K, Paemen L, Masure S, et al. Prevention of acute autoimmune encephalomyelitis and abrogation of relapses in murine models of multiple sclerosis by the protease inhibitor D-penicillamine. *Inflamm Res* 1995; 44:529-34.
55. Zuckerman AJ. Editor. Prevention of hepatitis B in the newborn, children, and adolescents. Royal College of Physicians London, UK 1996; 113.

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## **BIBLIOGRAPHY**

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1. Kass EH, Lichstein HC, Waisbren BA. Occurrence of hyaluronidase and lecithinase in relation to virulence in *Clostridium welchii*. *Proc Soc Exper Biol & Med*, 1945. 58:172-75.
2. Kass EH, Waisbren BA. A method for the consistent induction of chronic hyperglycemia with alloxan. *Proc Soc Exper Biol & Med*, Nov 1945. 60:303-6.
3. Waisbren BA, Vollmer EP. The effect of alloxan diabetes on susceptibility to streptococcal and pneumococcal infection in Swiss mice. *Naval Med Res Bull MM*, 1948. 7-24.
4. Waisbren BA. Alloxan diabetes in mice. *Proc Soc Exper Biol & Med*, Feb 1948. 67:154-56.
5. Waisbren BA, Hueckel JS. Reduced absorption of aureomycin caused by aluminum hydroxide gel (Amphojel). *Proc Soc Exper Biol & Med*, 1950. 73:73-74.
6. Waisbren BA, Spink WW. Comparative action of aureomycin, chloromycetin, neomycin, Q-19, and polymyxin B against gram-negative bacilli. *Proc Soc Exper Biol & Med*, May 1950. 74:35-40.
7. Waisbren BA, Spink WW. A clinical appraisal of neomycin. *Ann Int Med*, Nov 1950. 33#5:1099-1119.
8. Waisbren BA, Glick D. Effect of aureomycin on heparin concentration and clotting time of human blood. *Proc Soc Exper Biol & Med*, Nov 1950. 75:476-77.
9. Waisbren BA, Carr C, and Dunnette J. The tube dilution method of determining bacterial sensitivity to antibiotics. *Am J Clin Path*, Sep 1951. 21:884-91.
10. Waisbren BA. Bacteremia due to gram-negative bacilli other than the salmonella: A clinical and therapeutic study. *Arch Int Med*, Oct 1951. 88:467-88.
11. Waisbren BA, Carr C, and Struxness D. Role of inhibitors and mutations in antibiotic resistance by *escherichia coli*. *Antibiot & Chemother*, Nov 1951. 1 #8:534-39.
12. Spero L, Waisbren BA, Schantz EJ, Victor J. Mechanism of mucin activity. *Federation Proc* 1951. 10:371.
13. Hayford WD, Waisbren BA. Effect of the simultaneous oral administration of aureomycin and aluminum hydroxide gel on fecal urobilinogen. *Surg*, Mar 1952. 31 #3:361-64.

14. Waisbren BA, Carr CA. Penicillin and chloramphenicol in the treatment of infections due to proteus organisms. *Am J Med Sci*, Apr 1952. 223:418-21
15. Triantaphyllopoulos DC, Waisbren BA. Lack of influence of penicillin on blood coagulation. *Arch Int Med*, Nov 1952. 90:653-59.
16. Waisbren BA. A case of severe proteus bacteremia treated successfully with large doses of penicillin. *J Lab & Clin Med*, Dec 1952. 40:957-58.
17. Waisbren BA. Treatment with large doses of penicillin in case of severe bacteremia due to proteus. *Arch Int Med*, Jan 1953. 91:138-41.
18. Waisbren BA, Hastings EV. Bacterial endocarditis due to pseudomonas aeruginosa. *Arch Path*, Mar 1953. 55:218-22.
19. Erwin CP, Waisbren BA, Kruse R. Clinical and laboratory studies of infection due to pseudomonas aeruginosa and Pseudomonas species. *Am J Med Sci*, Nov 1953. 226:525-32.
20. Waisbren BA. A chromosome map of micrococcus pyogenes based on determinations of the sensitivities of individual strains of antibiotics. *J Lab & Clin Med*, Dec 1953. 42:960.
21. Hotter JT, Waisbren BA. The ineffectiveness of CID-545, a synthetic analog of chloramphenicol that does not contain a nitrobenzene ring. *Antibiot & Chemother*, Jan 1954. 4 #1:62-64.
22. Waisbren BA. Antibiotic treatment of bacterial endocarditis due to enterococcus: Presentation of a case and in-vitro studies that show a potentiating effect of erythromycin, chlortetracycline, and streptomycin on some strains of enterococci. *Arch Int Med*, Nov 1954. 94:846-52.
23. Waisbren BA. Bacterial resistance to antimicrobial agents. *International Forum* 3 #6:164-66.
24. Waisbren BA. The combination of erythromycin and chlortetracycline for the treatment of bacterial endocarditis. *J Lab & Clin Med*, Dec 1954. 44 #6:945.
25. Appleton DM, Waisbren BA. The prophylactic use of chloramphenicol in transurethral resections of the prostate gland. *J Urol*, Feb 1956. 75 #2:304-13.
26. Waisbren BA, Crowley W. Nitrofurantoin. *Arch Int Med*, May 1955. 95:653-61.
27. Waisbren BA. In vitro activity against micrococcus pyogenes of various combinations of antimicrobial agents. *J Lab & Clin Med*, Oct 1955. 46 #4:583-91.

28. Waisbren BA. The comparative sensitivities of gram-negative bacilli to the antibiotics. *J Lab & Clin Med*, Dec 1955. 46 #6:961
29. Waisbren BA. Introduction to the section on the clinical uses of neomycin, with exemplary case reports: Neomycin, its nature and practical application. Waksman SA 1958, Baltimore, Williams & Wilkins, P. 157-65.
30. Waisbren BA. Neomycin. *The Practitioner*, Jan 1956. 176:39-46.
31. Belli J, Waisbren BA. The number of blood cultures necessary to diagnose most cases of bacterial endocarditis. *Am J Med Sci*, Sep 1956. 232 #3:284-88.
32. Cherniss EI, Waisbren BA. North American blastomycosis: A clinical study of 40 cases. *Ann Int Med*, Jan 1956. 44:105-23.
33. Waisbren BA, Strelitzer CL. A five year study of the antibiotic sensitivities and cross resistances of staphylococci in a general hospital. *Antibiot Annual*, 1957-1958. 350-64.
34. Waisbren BA. The treatment of bacterial infections with the combination of antibiotics and gamma globulin. *Antibiot & Chemother*, Jun 1957. 7 #6:322-33.
35. Waisbren BA, Strelitzer CL. The sensitivities and cross resistances of gram-negative bacilli to antibiotics. *Arch Int Med*, May 1957. 99:744-50.
36. Waisbren BA. The *Proteus* produced inhibitor to nitrofurantoin. *Antibiot & Chemother*, Nov 1957. 7 #11:586-92.
37. Waisbren BA, Strelitzer CL. The sensitivity of staphylococci to antibiotics. *Arch Int Med*, Feb 1958. 101:397-406.
38. Waisbren BA. Current concepts in therapy. *New Eng J Med*, June 1958. 258:1213-15.
39. Wilcox KR Jr, Waisbren BA, Martin J. The Walworth, Wisconsin epidemic of histoplasmosis. *Ann Int Med*, Aug 1958. 49 #2:388-417.
40. Waisbren BA, Strelitzer CL. Antibiotic sensitivities of staphylococci isolated before and after patients were given antibiotics. *Am J Med Sci*, Aug 1959. 238 #2:202-10.
41. Abboud FM, Waisbren BA. Correlation between in-vitro studies and response to antibiotic therapy in staphylococcic bacteremia. *Arch Int Med*, Aug 1959. 104:226-33.
42. Waisbren BA, Erlandson AL, Fischer MW. Severe infections in adults caused by mouse-virulent stains of *escherichia coli*. *New Eng J Med*, Nov 1959. 261:1056-58.

43. Babbitt DP, Waisbren BA. Epidemic pulmonary histoplasmosis. *Am J Roentgen, Radium Therapy, & Nuc Med*, Feb 1960. 83 #2:236-50.
44. Waisbren BA, Abboud FM. Bacteremia due to coagulase-positive staphylococcus aureus. *Ann Int Med*, Mar 1960. 52 #3:643-76.
45. Waisbren BA. Pyogenic osteomyelitis and arthritis of the spine treated with combinations of antibiotics and gamma globulin. *J Bone & Joint Surg*, Apr 1960. 42-A #3:414-29.
46. Waisbren BA, Kleinerman L, Skemp J, Bratcher G. Comparative clinical effectiveness and toxicity of vancomycin, ristocetin and kanamycin. *Arch Int Med*, Aug 1960. 106:179-93.
47. Waisbren BA. The fifteen important pathogenic bacteria. *WI Med J*, Jul 1960. 59 #7:415-20.
48. Waisbren BA, Strelitzer CL. In-vitro activity and cross relationships of antibiotics with staphylococci and gram-negative bacilli. *Antibiot & Chemo*, Sep 1960. 10 #9:545-55.
49. Botticelli JT, Waisbren BA. Tetanus in an urban community. *Am J Med Sci*, Jul 1961. 242 #1:44-50.
50. Waisbren BA. The medical approach to patients with severe burns. *WI Med J*, Sep 1961. 60:475-480.
51. Henschel EO, Waisbren BA, Glaser M. Lung abscess as seen in a municipal hospital. *Dis Chest*, Dec 1961. 40 #6:625-31.
52. Waisbren BA, Brown I. Some aspects of the interactivity of staphylococci and the penicillins. *Antibiot & Chemo*, Feb 1962. 12 #2:97-102.
53. Waisbren BA, Brown I. The bactericidal activity of human serum against escherichia coli. *J Immuno*, Feb 1962. 88 #2:249-55.
54. Waisbren BA, Ullrich D. An isolated blastomycetoma of the posterior cranial fossa treated successfully with surgery and amphotericin B. *Am J Med*, Apr 1962. 32 #4:621-24.
55. Waisbren BA, Lepley D Jr. Antibiotics and gamma globulin in pseudomonas infections. *Arch Int Med*, Jun 1962. 109:712-16.
56. Waisbren BA, Simski C, Chang PL. Administration of maximum doses of chloramphenicol. *Am J Med Sci*, Jan 1963. 245 #1:35-45.
57. Erlandson AL, Fischer MW, Gagliardi LA, Pearson IA, Waisbren BA. Characteristics of strains of escherichia coli associated with severe infections in adults. *J Inf Dis*, 1961. 108:189-94.

58. Bennett IL, Finland M, Hamburger M, Kass EH, Lepper M, Waisbren BA. The effectiveness of hydrocortisone in the management of severe infections. A double-blind study. JAMA Feb 1963. 183 #6:462-65.
59. Collentine GE Jr, Conway JD, Woloschek W, Waisbren BA. Two years' experience in treatment of burns in a private general hospital. WI Med J, 1962. 61 #10:511-16.
60. Waisbren BA, Brown I. Inhibition of the bactericidal activity of human sera by wide-spectrum antibiotics. Antimicrob Agents & Chemo, 1963. 736-40.
61. Waisbren BA. Editorial. Gram-negative shock and endotoxin shock. Am J Med, 1964. 36 #6:819-24.
62. Waisbren BA, Brown I. Effect of wide-spectrum antibiotics on bactericidal activity of human serum: In-vitro and in-vivo. Am J Med Sci, July 1964. 248 #1:56-60.
63. Waisbren BA, Arena J. Shock associated with bacteremia due to gram-negative bacilli. Arch Int Med, Sept 1965. 116:336-39.
64. Waisbren BA. The proof of efficacy of antibiotics. Am J Med Sci, Oct 1965. 250 #4:406-23.
65. Waisbren BA, Hainer JW, Lutsky I, Tsagaris T. Abstract: Gram-negative bacteremia in dogs. Ann Int Med, 1965. 62 #5:1089.
66. Waisbren BA, Brown I. A factor in the serum of patients with persisting infection that inhibits the bactericidal activity of normal serum against the organism that is causing the infection. J Immuno, 1966. 97 #3:431-37.
67. Waisbren BA. Control of sepsis in burns. Trauma, 1967. 7:105-8.
68. Collentine GE, Waisbren BA, Melender JW. Treatment of burns with intensive antibiotic therapy and exposure. JAMA, June 12, 1967. 200 #11:939-42.
69. Waisbren BA. An essay regarding pathogenesis and treatment of shock due to bacteremia with special reference to "gram-negative" shock. Prog Cardiovas Dis, Sep 1967. 10 #2:123-33.
70. de Ycaza MM, Waisbren BA, Goodman JS. Therapy of bacterial endocarditis in penicillin-hypersensitive patients. Arch Int Med, Sept 1967. 120:361-64.
71. Waisbren BA, Hensley G, Lutsky I, Farmer S. Abstract: Experimental interstitial nephritis in the dog. J Clin & Lab Med, 1967. 70:989.
72. Waisbren BA. Lincomycin in larger doses. JAMA, Nov 25, 1968. 206 #9:2118.



73. Tsagaris T, Hainer J, Waisbren BA, Lange RL. The hemodynamic response to endotoxin in escherichia coli-resistant animals. *Am J Physiol*, 1969. 216:271-75.
74. Bermudez RH, Waisbren BA. Activity of chloramphenicol against *Escherichia coli* circulating in the blood and tissues of immunized dogs. *Antimicrob Ag & Chemo*, 1968. 511-14.
75. Waisbren BA. Experiences with the new antibiotic gentamicin. *J Inf Dis*, Apr 1969. 119 #4:518-27.
76. Waisbren BA. Intensive treatment of infections with antibiotics, intravenous gamma globulin, and aggressive therapy. *Med Counterpoint*, Jan 1970. 2:23-32.
77. Waisbren BA. Meeting the challenge of critical care medicine. *WI Med J*, 1970. 69:197-200.
78. Waisbren BA. Antibiotics in the treatment of burns. *Surg Clin N.A.*, Dec 1970. 50 #6:1311-23.
79. Waisbren BA. Patient oriented, M.D. - designed hospital. *Med Opinion & Rev*, Jul 1970. 6 #7:209-14.
80. Waisbren BA. Designing a modern hospital: A physician's point of view. Delaware Med J adapted form presentation the Wilmington Med Ctr Conf, May 26, 1970.
81. Waisbren BA, Kurzynski TA, Mellender JW. Studies of *pseudomonas aeruginosa* - the burn pathogen. Research in burns, Hans Huber Publishers, Bern Stuttgart, Vienna, 1970. Trans of 3rd Int'l Congress on Research.
82. Waisbren BA, Mellender JW, Collentine GE. Burn mortality with treatment by parenteral and local antibiotics and total exposure. Hans Huber Publishers, Bern, Stuttgart, Vienna, 1970. Trans of 3rd Int'l Congress on Research.
83. Collentine GE, Waisbren BA, Lang GE. Inappropriate secretion of antidiuretic hormone as an accompaniment of burn injury. Hans Huber Publishers, Bern, Stuttgart, Vienna, 1970. Trans of 3rd Int'l Congress on Research.
84. Singhi S, Waisbren BA, Becker IM. Granulomatous ileocolitis with multiple fistulae treated with gut rest, hyperalimentation, and antibiotics. *WI Med J*, May 1972. 71:152-54.
85. Walker WE, Waisbren BA, Martins RR, Batayias GE. In-vitro determinations of viral susceptibility to drugs for possible clinical use. *Antimicrob Ag & Chemo*, 1970. 380-84



86. Waisbren BA, Evani SV, Ziebert AP. Carbenicillin and bleeding. JAMA, Aug 30, 1971. 217 #9:1243.
87. Bortin MM, Saltzstein EC, Waisbren BA, Kay SA Hong R, Bach FH. Bone marrow transplantation for aplastic anemia. Transplantation, Jun 1971. 12 #6:573-75.
88. Walker WE, Waisbren BA, Martins RR, Batayias GE. A method for determining sensitivities of antiviral drugs in-vitro for possible use as clinical consultation. Am J Clin Path, Dec 1971. 56 #6:687-92.
89. Waisbren BA. Care of the critically ill: The systems method. Hosp Med Staff, Feb 1972. 1.
90. Waisbren BA. The total management of the burned patient. J St Barnabas Med Ctr, July 1972. 9 #1:1-10.
91. Waisbren BA. The function of the hospital environment in the human endeavor. Arch Int Med, Nov 1972. 130:785-88.
92. Downes JJ, Del Guercio L, Grace WJ. Pontoppidan H, and Waisbren BA. Guidelines for organization of critical care units. JAMA, Dec 1972. 222:1532-35.
93. Waisbren BA. Toward a mission-oriented medical record system. Crit Care Med, Sept-Oct 1973. 1 #5:261-66.
94. Waisbren BA, Martins RR, Bruns WT, Kurzynski TA. Whole cell heat-killed gram-negative bacilli vaccine. WI Med J, Apr 1974. 73:42-45.
95. Apfelberg DB, Waisbren BA, Masters FW, Robinson DW. Treatment of chondritis in the burned ear by the local instillation of antibiotics. Plast & Reconst Surg, Feb 1974. 53 #2:179-83.
96. Waisbren BA, Walzl, FL. Paresis and the priest: James Joyce's symbolic use of syphilis in "The Sisters." Ann Int Med, June 1974. 80 #6:758-62.
97. Guttman RM, Waisbren BA. Bacterial blocking activity of specific IgG in chronic pseudomonas aeruginosa infection. Clin Exp Immunol, 1975. 19:121-30.
98. Waisbren BA, Stern M, Collentine GE. Methods of burn treatment: Comparison by probit analysis. JAMA, Jan 20, 1975. 231:255-58.
99. Waisbren BA. The Rabelaisian school of treating severe infections - a hopeful paradigm. Crit Care Med, 1975. 3 #3:118-22.
100. Waisbren BA. Treatment of severe burns. Comp Ther, Jan 1976. 2:33-42.

101. Stern M, Waisbren BA. A method by which burn units may compare their results with a base line curve. Surg, GYN & OB, Feb 1976. 142:230-34.
102. Waisbren BA. Simultaneous multiple organ support. Hosp Pract, May 1976. 102-12.
103. Waisbren BA. Editorial: Standardizing units of measurements. JAMA, Oct 25, 1976. 236 #17:1981-82.
104. Waisbren BA. School-hospital affiliations: A balancing of interests. Hosp Pract, Jun 1977. 117-24.
105. Klein, RA, Waisbren BA, Welsh GJ. State or regional critical care societies. Crit Care Med, 1977. 5 #4:204-6.
106. Waisbren BA. Critical Care Manual, a systems approach method. Medical Examination Pub Co Inc, Flushing NY 2nd Ed, 1977.
107. Waisbren BA. Some serendipitous results of the practice of investigative internal medicine. WI Med J, Jan 1978. 77:1-4.
108. Waisbren BA, Smith MB. Editorial: Hypersensitivity to meperidine. JAMA, Apr 3, 1978. 239 #14:1395.
109. Waisbren BA. Home accident prevention manual. Grosset & Dunlap Inc NY 1978.
110. Waisbren BA. Infection control in total parenteral nutrition. Arch Int Med, Jul 1978. 130 #7:1175.
111. Waisbren BA. A paradigm that explains gram-negative shock. Am J Med, Sep 1978. 65:403-5.
112. Waisbren BA, Stern M, Collentine GE. Data for comparative study from a burns centre. Burns, 1978. 5:30-35.
113. Waisbren BA, Hurley DJ, Siegesmund KA, Guttman RM. Morphologic expression of the interactions of human lymphocytes and pseudomonas aeruginosa as observed by scanning electron microscopy. J Inf Dis, Jan 1979. 139 #1:18-25.
114. Waisbren BA. Emergency care manual. Medical Examination Pub Co Inc, Flushing NY 1979.
115. Hurley DJ, Waisbren BA, Guttman RM, Siegesmund KA. Human lymphocyte-tumor cell interaction: A scanning electron microscopy study. JAMA, Jun 15, 1979. 241 #24:2631-33.

116. Stern M, Waisbren BA. Comparison of methods of predicting burn mortality. Scand J Plas Recon Surg, 1979. 13:201-4.
117. Waisbren BA, Hurley D. Potential of direction observation of human lymphocyte-tumor cell interactions in the scanning electron microscope as a means of evaluating cancer therapy. Reprinted from Cur Chemo & Inf Dis Proceedings of the 11th ICC and 19th ICAAC, American Society of Microbiology, 1980.
118. Hall V, Waisbren BA. Syphilis as a major theme of James Joyce's "Ulysses." Arch Int Med, Jul 1980. 140:963-65
119. Waisbren BA. Realities of critical care medicine - present and future. J Med Soc of New Jersey, Nov 1980. 77 #12:803-6
120. Waisbren SJ, Hurley DJ, Waisbren BA. Morphological expressions of antibiotic synergism against pseudomonas aeruginosa as observed by scanning electron microscopy. Antimicrob Ag & Chemo, Dec 1980. 18 #6:969-75
121. Waisbren BA, Schutz D, Collentine GE, Banaszak E, Stern M. Hyperbaric oxygen in severe burns. Burns, Jan 1982. 8 #3:176-79.
122. Milson TJ Jr, Waisbren BA, Makiya RK. Suppressor T-cells in peripheral blood. Clin Res, 1982. 30 #4:776A.
123. Waisbren BA. Swine influenza vaccine. Ann Int Med, Jul 1982. 97 #1:149.
124. Yarborough GW, Waisbren BA. The benefits of systematic fiberoptic flexible sigmoidoscopy. Arch Int Med, Jan 1985. 145:95-96.
125. Waisbren BA. Aging and its lessons regarding the future approach to burns which are not fatal. Presented at the 25th Anniversary seminar of St. Mary's Burn Center, Aug 1984. The Bulletin & Clinical Review of Burn Injuries, Jul, Aug, Sep 1985. 11 #3:36-37.
126. Waisbren BA. Personal experience in hyperbaric oxygen therapy in a general hospital setting - special emphasis on therapy of infected joint prosthesis and hidradenitis suppurativa. Presented at International Symposium on Hyperbaric Oxygen in Critical Care Medicine, Jun 1985.
127. Waisbren BA. Sinusitis. Current therapy in internal medicine - 2, 1987. 204-6.
128. Waisbren BA. Point of View: Observations on the combined systemic administration of mixed bacterial vaccine, bacillus calmette-guerin, transfer factor, and lymphoblastoid lymphocytes to patients with cancer, 1974-85. J Biol Resp Mod, 1987. 6:1-19.

129. Waisbren BA, Cashman N, Schell RF, Johnson R. *Borrelia burgdorferi* antibodies and amyotrophic lateral sclerosis. *Lancet*, Aug 1987. 2:332.
130. Waisbren BA. Other side of the coin. *Inf Dis News* Sep 1992 5:#9.
131. Waisbren BA. New therapies for multiple sclerosis - When? *WI Med J*, Aug 1993. 9 #8:448-50.
132. Waisbren BA. Anti-thrush popsicles. *Courtlandt Forum*, Oct 1993. 6 #10:71.
133. Waisbren BA. Universal hepatitis B vaccinations. *WI Med J*, Mar 1996. 95 #3:148.
134. Waisbren BA. Perspectives on hepatitis B vaccination. *JAMA* April 9, 1997. 227 #14:1124.